

Supplementary Materials and Methods

TALEN construction and microinjection. Transcription activator-like effector nucleases (TALENs) are designed using a TALEN design website Mojo Hand (www.talendesign.org; more recent version at www.talendesign.org/betatest/)¹. The sequences of TALENs are provided in Table S3. Designed TALENs are assembled following the Golden Gate methods²⁻⁴ in a single-tube reaction using the FusX kit⁵. In this single-tube reaction, the component plasmids are cloned into the destination vector, pT3TS-FokI, in a Golden Gate reaction. Constructed TALEN plasmids are validated through Sanger sequencing with sequencing primers: TAL_Seq_5-1 (5'-catcgcaatgcactgac) and TAL_R2 (5'-ggcgacgagggtggcgtgg). After the sequence is confirmed, TALEN plasmids are linearized with SacI-HF® (NEB) and confirmed on 1% agarose gel. Linearized TALEN plasmids are *in vitro* transcribed to mRNA using mMessage mMachine® T3 Transcription Kit (Thermo Fisher Scientific Inc.). Transcribed mRNA is verified on a 1% agarose gel to quickly assess its concentration and quality, which is compared to measurements made with a spectrophotometer (NanoDrop 2000, Thermo Fisher Scientific Inc.). For microinjection, the tip of a pulled glass pipet is broken using forceps under dissecting microscope and used to deliver 25–75 pg of mRNA in a volume of approximately 1 nL using a pico liter injector (PLI-90, Harvard Apparatus).

Derivation of mutant zebrafish strains. The embryos injected with TALENs are prescreened to assess TALEN activity as previously described⁶. Embryo clutches (F0) injected with active TALEN pairs were raised to adults, then out-crossed to SWT. 14–20 embryos among spawned F1 embryos were assessed through RFLP for the rate of germline transmission. The embryo clutches that showed a high rate of germline transmission were raised to obtain the F1 generation. Tailfin biopsy was performed on adult F1 fish by clipping the tip of the tailfin to survey germline mutations transmitted to different individual fish. Two frame-shift variants (base deletions and/or insertions that are not multiples of 3) for each injected TALEN pair were raised to adulthood to cross-validate mutant phenotypes for the mutated gene. These selected F1 zebrafish that carry a desired mutant variant was out-crossed with SWT to obtain F2 and further generations to clean out potential background mutations. Continuous out-crossing is performed and all behavioral assays are performed with F2 or later generation zebrafish. All adult zebrafish stock is maintained as heterozygous.

Cortisol extraction and enzyme-linked immunosorbent assay. After experiments, larval zebrafish are rapidly collected using custom-made collecting devices and funnels in 900 µL of phosphate buffered saline (PBS; 1x). Because we purported to discern the changing cortisol levels in minutes of intervals, rapidly collecting the samples within a one-minute window was critical. Custom collecting devices are made by gluing a small sized baffle (400 micron, ZT280S400, Aquaneering Inc.) to a 15 mL conical tube crosssectionally cut in half. Using multiples of the devices, several samples are effectively collected within a one-minute time window. Collected samples are snap-frozen in liquid nitrogen and stored at -80°C after the sample collection is completed.

Samples are thawed on ice on the day of cortisol extraction. Thawed samples are transferred to 12 mL glass test tubes and homogenized on ice with an ultrasonic processor (Vibra-Cell VCX 130, Sonics and Materials Inc.). The regimen for homogenization of each sample is pulse-on for 1 sec and pulse-off for 1 sec for a total of 480 sec at an amplification setting of 32%. The regimen for washing the sonicator probe after processing each sample is pulse-on and pulse-off for 20 sec in ultrapure water, pulse-on and pulse-off for 20 sec in ethanol (100%), and pulse-on and pulse-off for 20 sec in ultrapure water. Cortisol is extracted from 650 µL of the homogenate three times using 3 mL of diethyl ether each time (Thermo Fisher Scientific Inc.). Ether is

evaporated in a water bath at 42°C for 4–5h (or overnight), and the samples are reconstituted in 500 µL of PBS (1x) at 4°C for 2–3h with occasional vortexing.

After extraction, cortisol in each sample is quantified with a cortisol enzyme-linked immunosorbent assay (ELISA) kit (Cortisol ELISA Kit, Cayman Chemical). The cortisol level in each sample is normalized to the amount of protein quantified in a bicinchoninic acid-based assay (Pierce BCA Protein Assay Kit, Thermo Fisher Scientific Inc.) using a 25 µL of sample homogenate. The cortisol extraction efficiency using this method is approximately 70%, and the calculated extraction efficiency is used to convert the quantified cortisol levels to the actual amount of cortisol per sample.

Allele-specific quantitative polymerase chain reaction (ASQ) genotyping. Allele-specific quantitative PCR (ASQ) was developed to effectively handle a large volume of genotyping, often over 600 samples, after behavioral assays are performed⁷. Genotyping is conducted following the protocol in the paper. The primer and probe sequences are provided in Table S4.

Behavioral assays with drugs. Behavioral assays (light or cinnamon oil) with pharmacological agents were performed following the same protocol as light or cinnamon oil assays. Drugs are applied between 4 and 5 dpf and behavioral assays are done with drugs in water. Larval fish are incubated in the drug for 12-16 h on average by the time an assay is performed.

Supplemental Figure Legend

Fig. S1. Spectrograms of light illumination. The intensities of white or infrared light were measured at each wavelength using a miniature spectrometer (STS-VIS or STS-NIR; Ocean Optics, Inc.). The graphs were generated by OceanView spectroscopy software (ver. 1.5.0; Ocean Optics, Inc.). (A) White light at the High intensity setting of the Light Box shows the wavelength distribution between approximately 430 to 710 nm with the peak intensity level at around 1300. White light at the High intensity was used for white light illumination during the dual light assays. (B) White light at the Medium intensity setting in the Light Box shows the same wavelength distribution with the decreased peak intensity at around 650. White light at the Medium intensity was used as white light illumination during the hyperosmotic (NaCl) or cinnamon oil assays. (C) Infrared light at the High intensity shows the wavelength distribution between approximately 790 and 880 nm with the peak intensity level at around 450. Infrared light was used during the dual light assay.

Supplemental Table 1. Materials

Materials/Instruments	Cat. No	Vendor	Address
2-amino-2-(hydroxymethyl)-1,3-propanediol (Tris)	T1378	Sigma-Aldrich Co. LLC.	St. Louis, MO, USA
48-well plates	08-772-1C	Falcon	Waltham, MA, USA
5x MyTaq™ Reaction Buffer Colorless	BIO-37111	Bioline USA Inc.	Taunton, ME, USA
5x MyTaqTM Red Reaction Buffer	BIO-37112	Bioline USA Inc.	Taunton, ME, USA
ASQ Fluorescent probes and quenchers	-	IDT, Inc.	Coralville, IA, USA
Baffle / Screen (400 µm)	ZT280S400	Aquaneering, Inc.	San Diego, CA, USA
Benchtop Optical Power Meter	1936-R	Newport Corp.	Irvine, CA, USA
CFX96 C1000 Touch™	185-5096	Bio-Rad Laboratories, Inc.	Hercules, CA, USA
Cortisol ELISA Kit	500360	Cayman Chemical	Ann Arbor, MI, USA
Crossing tanks (1 L)	ZHCT100	Aquaneering, Inc.	San Diego, CA, USA
DC12V SMD3528-600-IR InfraRed Single Chip	HK-F3528IR60-	LED Lights World LTD.	Shenzhen, GuangDong, China
Flexible LED Strips 120L EDs 9.6W Per Meter	X		
Diethyl ether	AC615080010	Acros organics	Waltham, MA, USA
Ethylenediaminetetraacetic acid disodium salt dihydrate (EDTA)	E-5134	Sigma-Aldrich Co. LLC.	St. Louis, MO, USA
Handycam	HDR-CX560V	Sony Corp.	New York City, NY, USA
Housing tanks (3, 9 L)	ZT280, 950	Aquaneering, Inc.	San Diego, CA, USA
Light box with white LED strips (40W)*	LPW-xW6060-40	Super Bright LEDs Inc.	St. Louis, MO, USA
Light boxes*	-	Division of Engineering, Mayo Clinic	Rochester, MN, USA
Pico liter injector (PLI-90)	EC1 65-0004	Harvard Apparatus	Holliston, MA, USA
Microseal® 'B' seal	MSB1001	Bio-Rad Laboratories, Inc.	Hercules, CA, USA
Miniature spectrometer	STS-VIS & STS-NIR	Ocean Optics Inc.	Largo, FL, USA
mMESSAGE mMACHINE® T3 Transcription Kit	AM1348	Ambion	Waltham, MA, USA
Multiplate™ PCR plates 96-well, clear	MLL9601	Bio-Rad Laboratories, Inc.	Hercules, CA, USA
MyTaq™ DNA Polymerase	BIO-21106	Bioline USA Inc.	Taunton, ME, USA
MyTaq™ HS DNA Polymerase (5 units/µL)	BIO-21111	Bioline USA Inc.	Taunton, ME, USA
NanoDrop 2000	-	Thermo Fisher Scientific Inc.	Waltham, MA, USA
Pierce™ BCA Protein Assay Kit	23225	Thermo Fisher Scientific, Inc.	Waltham, MA, USA
Random primers	48190011	Thermo Fisher Scientific, Inc.	Waltham, MA, USA
Restriction endonuclease	-	New England Biolabs, Inc.	Ipswich, MA, USA
Round gel loading tip	NC9531852	Fisher scientific	Waltham, MA, USA
SensiFAST™ SYBR® No-ROX Kit	BIO-98005	Bioline USA Inc.	Taunton, ME, USA
Microloader pipette tips	E5242956003	Fisher Scientific	Waltham, MA, USA
Sodium chloride (NaCl)	S9888	Sigma-Aldrich Co. LLC.	St. Louis, MO, USA
Sodium hydroxide, Pellets (NaOH)	7708	Mallinckrodt Limited	Mulhuddart, Dublin 15, Ireland
SuperScript™ II Reverse Transcriptase	18064014	Invitrogen	Waltham, MA, USA
T100™ Thermal Cycler	186-1096	Bio-Rad Laboratories, Inc.	Hercules, CA, USA
TaqMan Probes™	-	Applied Biosystems™	Waltham, MA, USA
Vibra-Cell VCX 130 (sonicator)	VCX 130	Sonics and Materials Inc.	Newtown, CT, USA
VorTemp™ 56 shaking incubator	S2056A	Labnet International, Inc.	Edison, NJ, USA

*Several units of light boxes with white LED strips were purchased from Super Bright LEDs Inc. and engineered to have dual light sources and a control panel to meet research needs. Safety requirements per Mayo Clinic policy have been met. The Mayo Clinic Division of Engineering engineered and produced the custom light boxes.

Supplemental Table 2. Zebrafish mutant variants in the paper

Colon (:) denotes "deletion." **Bold**, underlined, **blue**, *italicized*, lower case **bases** denote "substitution." **Bold**, underlined **bases** denote "insertion."

“mn” is the official allele designator for the Mayo Clinic with Zebrafish Information Network (<http://zfin.org/action/feature/line-designations>).

Supplemental Table 3. Transcription activator-like effector nuclease (TALEN) target sequences

Locus	Name	Sequence
<i>mc2r</i> exon 2	mc2r_TAL2_F (16-mer)	5'—ATCATGGACTCTTAC
	mc2r_TAL2_R (15-mer)	5'—GCTGAAGATTGAACC
<i>nr3c1</i> exon 2	nr3c1_ex2_TAL1_F (15-mer)	5'—TTGGAACAGCTCGC
	nr3c1_ex2_TAL1_R (15-mer)	5'—GATCTTCTGCAGAC
<i>nr3c1</i> exon 5	nr3c1_ex5_TAL1_F (15-mer)	5'—GGTGCCAAACC <u>C</u> AT
	nr3c1_ex5_TAL1_R (15-mer)	5'—AGTGATAGCATAGTG
<i>nr3c2</i> exon 2	nr3c2_TAL2_F (15-mer)	5'—GGGCTGCTTCCTTC
	nr3c2_TAL2_R (16-mer)	5'—ATCCCCTCAAAGACAAG

Bold, underlined, red, italicized, lower case **bases** denote polymorphisms that deviate from the zebrafish reference sequences in our fish stock.

Supplemental Table 4. Reagents for restriction fragment length polymorphism (RFLP) genotyping and allele specific qPCR (ASQ) genotyping

Locus	Reagent	Sequence
<i>mc2r</i>	TSNP_mc2r_F1	5'—CTGAATCTCCCTCCAGCATCCACA
	TSNP_mc2r_R1	5'—CTGCCTCAAAAAAGCCGACCATTAG
	Restriction endonuclease	NspI
RFLP	TSNP_nr3c1ex2_F2	5'—CCCCAGGGGTCATCAAACAGG
	TSNP_nr3c1ex2_R2	5'—ACATTACACGAACATCGCATTCAAC
	Restriction endonuclease	PvuII-HF
<i>nr3c1ex5</i>	TSNP_nr3c1ex5_F2	5'—GCACGTCAAGCCGGAAAG
	TSNP_nr3c1ex5_R2	5'—GGAACACTGCAGGAGGGTC
	Restriction endonuclease	PvuII-HF
<i>nr3c2ex2</i>	nr3c2_TAL2_F	5'—GAGTTCCCGAAGGTAGAGAATG
	nr3c2_TAL2_R	5'—CGCTCCAATCTGGTAATGAAATG
	Restriction endonuclease	BsaI
Fluorescent probes	Probe (FAM)	5'—FAM—AATGGCTTCCGAGACCTGCTGT <u>CATGGACTCTTACTCTGCATGTG</u>
	Probe (HEX)	5'—HEX—CGACAGAACACGCTCCAGCATTG <u>GATATCATGGACTCTTACTCTGCTTT</u>
Quencher	Quencher (FAM)	5'—GGTCTCGGAAGCCATT—BHQ
	Quencher (HEX)	5'—GAGCGTGTCTGT <u>CG-BHQ</u>
ASQ	WT	5'—AATGGCTTCCGAGACCTGCTGT <u>CATGGACTCTTACTCTGCATGTG</u>
	4del 1sub (mn57)	5'—CGACAGAACACGCTCCAGCATT <u>CGATATCATGGACTCTTACTCTGCTTT</u>
	4del 2sub (mn58)	5'—CGACAGAACACGCTCCAGCATT <u>CGATATCATGGACTCTTACTCTTACTTC</u>
	5 del (mn59)	5'—CGACAGAACACGCTCCAGCATT <u>GGATATCATGGACTCTTACTCTGCATTTC</u>
	Reverse	5'—TGCCTCAAAAAAGCCGACCATTAG
<i>nr3c1ex2</i>	WT	5'—AATGGCTTCCGAGACCTGCTGT <u>CTTCTGCAGACCGACGACAG</u>
	7 del (mn61)	5'—CGACAGAACACGCTCCAGCATT <u>GGCTTCTGCAGACCGACGTGG</u>
	17 del (mn62)	5'—CGACAGAACACGCTCCAGCATT <u>GGCTTCTGCAGACCGACGAGAAA</u>
<i>nr3c2ex2</i>	Reverse	5'—CCCCAGGGGTCATCAAACAGG
	WT (7 del)	5'—AATGGCTTCCGAGACCTGCTGT <u>CTGCTTCCCTCGACAGAGAC</u>
	7 del (mn66)	5'—CGACAGAACACGCTCCAGCATT <u>GCTGCTTCCCTCGACAGATACTT</u>
	WT (55 del)	5'—AATGGCTTCCGAGACCTGCTGT <u>CGGCTGCTTCCCTCGAC</u>
	55 del (mn67)	5'—CGACAGAACACGCTCCAGCATT <u>GGGCTGCTTCCCTCGGG</u>
	Reverse	5'—CCTGTTAATCCCCTGGCAGG

Supplemental Table 5. Locomotor response statistics of larval zebrafish: Light assays & NaCl assays

Genotype	Pre-condition	Tx	Before treatment		After treatment		n
			Locomotion (mm)	Std. dev.	Locomotion (mm)	Std. dev.	
WT	3 dpf		0.0488	0.21132	0.0774	0.1775	128
	4 dpf	White light	2.8119	5.93383	13.9024	17.77121	576
	5 dpf		2.0913	4.37076	14.2504	12.4384	425
<i>mc2r</i> WT			3.9441	5.02059	15.1573	13.23303	78
<i>mc2r</i> Het	None	White light	3.7745	5.24298	15.7878	13.68351	129
<i>mc2r</i> Hom			5.1405	7.92075	7.9485	7.12125	82
<i>nr3cl</i> ex2 WT			6.5379	5.9686	27.306	14.43307	136
<i>nr3cl</i> ex2 Het	None	White light	5.5306	6.58741	26.2521	13.84045	207
<i>nr3cl</i> ex2 Hom			6.2337	6.60818	17.5508	11.63806	109
<i>nr3cl</i> ex5 WT			5.04863	7.46703	18.9471	16.8750	212
<i>nr3cl</i> ex5 Het	None	White light	4.80090	5.98431	17.8811	15.0318	471
<i>nr3cl</i> ex5 Hom			4.02494	5.15557	12.5301	15.1481	254
<i>nr3c2</i> WT			3.11524	3.81495	14.4774	12.1189	115
<i>nr3c2</i> Het	None	White light	2.89014	3.84979	13.6531	10.0869	226
<i>nr3c2</i> Hom			3.48582	4.29183	14.8794	12.3984	93
WT	Veh		5.90843	5.91273	17.2969	13.1103	512
	Mif 5 µM	White light	6.48100	7.09852	15.7021	12.5571	261
	Mif 7.5 µM		6.07637	6.04605	7.64442	8.22950	343
	Mif 10 µM		3.13027	4.05568	3.62211	3.95047	327
WT	Veh		3.73387	4.08079	14.8120	12.9136	264
	Spr 5 µM	White light	5.02422	7.24691	17.5644	16.2770	264
	Spr 7.5 µM		5.14420	6.90128	18.6948	16.9627	264
	Spr 10 µM		2.99231	4.05520	16.3498	15.5966	258
WT	Veh		4.1322	10.14693	12.5043	12.47181	198
	Par 0.625 µM	White light	2.3078	5.69379	7.6353	8.44118	427
	Par 1.25 µM		1.9038	4.25809	5.2712	6.85558	405
WT	Veh		5.9389	5.86081	22.1074	14.68632	155
	Phe 10 µM	White light	10.4287	15.08525	30.8554	20.69626	150
	Phe 50 µM		10.4511	17.1527	31.5596	19.78768	149
	Phe 100 µM		10.4095	18.97596	28.5031	20.90262	147
WT	White light: 15 sec		3.393	4.30721	10.5314	9.14129	192
	White light: 30 sec		2.9119	4.16424	13.033	11.87452	307
	White light: 60 sec		2.0913	4.37076	14.2504	12.4384	425
	White light: 600 sec		6.0808	7.20349	22.3502	18.43711	96
	White light: 1800 sec		8.855	14.745	26.0159	17.53959	96
WT	Veh		14.8962	17.45642	19.1279	18.8023	96
	50 mM NaCl		11.3042	14.90575	26.1863	26.41791	48
	100 mM NaCl		15.6588	16.812	45.5946	26.42193	96
	150 mM NaCl		10.2486	11.81555	32.1659	25.83238	96
	200 mM NaCl		12.4327	10.99389	24.324	25.49064	48
<i>mc2r</i> WT	Veh		6.62376	15.83993	7.66119	15.54534	142
<i>mc2r</i> Het	Veh		7.24157	14.75820	9.23068	13.96416	231
<i>mc2r</i> Hom	None	Veh	3.69666	8.676138	4.20082	8.222990	111
<i>mc2r</i> WT		NaCl	9.11717	17.92911	32.67077	30.06965	129
<i>mc2r</i> Het		NaCl	8.33391	16.10090	28.17519	30.22601	243
<i>mc2r</i> Hom	NaCl		3.46139	8.919247	16.46409	22.32253	116
<i>nr3cl</i> ex2 WT	Veh		15.8727	30.58487	15.9509	28.06522	91
<i>nr3cl</i> ex2 Het	Veh		14.0539	26.5779	12.767	22.43097	185
<i>nr3cl</i> ex2 Hom	None	Veh	5.8909	13.49386	5.7474	13.00949	93
<i>nr3cl</i> ex2 WT		NaCl	13.741	26.28071	45.4379	42.58136	105
<i>nr3cl</i> ex2 Het		NaCl	11.7246	19.62243	42.3336	38.33053	179
<i>nr3cl</i> ex2 Hom	NaCl		5.1328	10.88953	39.1078	38.23013	87
<i>nr3cl</i> ex5 WT	Veh		12.2395	16.14661	13.4414	15.48458	44
<i>nr3cl</i> ex5 Het	Veh		11.3177	18.25093	13.9335	20.40939	94
<i>nr3cl</i> ex5 Hom	None	Veh	7.7049	16.38864	5.1057	7.8991	51
<i>nr3cl</i> ex5 WT		NaCl	7.3478	15.39785	37.1285	31.82217	46
<i>nr3cl</i> ex5 Het		NaCl	9.1891	15.24576	26.7721	27.513	107
<i>nr3cl</i> ex5 Hom	NaCl		6.6776	12.19779	23.4637	21.60652	41
<i>nr3c2</i> veh-inj	Veh		19.7437	27.32944	15.6914	27.21881	216
<i>nr3c2</i> TAL-inj	None	Veh	18.6963	29.72779	18.3992	30.27787	192
<i>nr3c2</i> veh-inj		NaCl	18.8544	30.65346	47.6213	40.43482	216
<i>nr3c2</i> TAL-inj	NaCl		19.1822	30.47587	50.2092	42.94021	204

* Mif (mifepristone), Spr (spironolactone), Par (paroxetine), Phe (phenylephrine). All NaCl treatment is 100 mM unless otherwise specified.

Supplemental Table 6. Locomotor response statistics of larval zebrafish: Cinnamon oil assays

Genotype	Pre-condition	Tx	Before treatment		After treatment		n
			Locomotion (mm)	Std. dev.	Locomotion (mm)	Std. dev.	
WT	3 dpf	Veh	0.0911	0.19245	0.0795	0.23236	80
	4 dpf	Veh	8.4682	20.58886	3.1934	9.7509	216
	5 dpf	Veh	41.1328	40.09287	23.9448	28.97232	286
	3 dpf	Cinn	0.1065	0.315	111.3485	47.29173	80
	4 dpf	Cinn	6.7395	16.02609	98.521	47.5726	360
	5 dpf	Cinn	36.0203	35.58338	92.0934	48.70159	270
<i>mc2r</i> WT		Veh	22.0074	33.83897	19.0271	26.64238	40
<i>mc2r</i> Het		Veh	18.4193	24.44073	17.9173	22.43415	104
<i>mc2r</i> Hom	None	Veh	15.9552	28.3973	13.3914	19.02287	47
<i>mc2r</i> WT		Cinn	23.321	21.40052	55.0662	49.72431	54
<i>mc2r</i> Het		Cinn	27.9722	31.55853	60.5981	52.69143	94
<i>mc2r</i> Hom		Cinn	24.9866	24.16921	49.4625	42.61792	44
<i>nr3cl</i> ex2 WT		Veh	30.8293	39.98468	28.7314	30.09043	81
<i>nr3cl</i> ex2 Het		Veh	29.0299	32.48255	26.4942	29.53706	156
<i>nr3cl</i> ex2 Hom	None	Veh	14.5311	22.58817	24.6218	26.44459	95
<i>nr3cl</i> ex2 WT		Cinn	31.1428	35.8568	102.996	59.83446	67
<i>nr3cl</i> ex2 Het		Cinn	25.2647	28.84129	107.5006	65.11712	178
<i>nr3cl</i> ex2 Hom		Cinn	21.7474	25.63352	97.3218	67.79751	89
<i>nr3cl</i> ex5 WT		Veh	15.2476	15.29052	18.2038	20.25472	50
<i>nr3cl</i> ex5 Het		Veh	20.5305	17.86791	23.4965	21.2174	99
<i>nr3cl</i> ex5 Hom	None	Veh	11.6407	11.16866	20.3377	16.81408	43
<i>nr3cl</i> ex5 WT		Cinn	19.4774	17.71868	63.0845	53.61833	53
<i>nr3cl</i> ex5 Het		Cinn	19.0184	26.07338	67.9984	54.89499	90
<i>nr3cl</i> ex5 Hom		Cinn	12.545	18.40385	63.9783	47.57266	48
WT	Veh	Veh	19.1001	23.14908	14.4056	20.02497	229
	Mif 5 μ M	Veh	16.3223	19.47182	10.7482	17.48589	111
	Mif 7.5 μ M	Veh	13.9347	17.38979	14.1497	12.31615	163
	Mif 10 μ M	Veh	3.862	6.17986	4.4823	6.50287	156
	Veh	Cinn	21.6156	24.54913	52.4068	31.16816	267
	Mif 5 μ M	Cinn	19.9321	22.55687	49.3295	25.18015	134
	Mif 7.5 μ M	Cinn	16.8555	17.75896	47.4124	22.0043	164
	Mif 10 μ M	Cinn	3.8364	6.42332	19.3237	16.27152	171
	Veh	Veh	24.7043	30.09589	15.0245	23.46978	132
	Spr 5 μ M	Veh	30.7927	38.01589	18.5624	26.66813	132
WT	Spr 10 μ M	Veh	24.4098	34.35553	15.7598	23.70551	132
	Spr 20 μ M	Veh	18.441	22.97198	13.5301	23.35744	126
	Veh	Cinn	25.7515	32.35167	56.4811	33.91568	132
	Spr 5 μ M	Cinn	25.0919	30.27707	65.4295	37.8229	132
	Spr 10 μ M	Cinn	24.0957	31.03932	60.0286	31.6415	132
	Spr 20 μ M	Cinn	14.1052	21.42619	45.6946	25.02714	132
	Veh	Veh	36.0718	35.35787	24.2394	29.04843	102
WT	Par 0.625 μ M	Veh	24.0816	33.4126	13.9719	25.03789	218
	Par 1.25 μ M	Veh	16.6703	22.58246	7.1356	17.56196	198
	Veh	Cinn	42.0821	39.0105	96.5756	44.13712	96
	Par 0.625 μ M	Cinn	21.7104	29.84018	95.5073	55.35021	215
	Par 1.25 μ M	Cinn	15.2084	24.09833	71.153	49.0064	201
WT	Veh	Veh	40.966	29.23554	27.5235	25.94815	78
	Phe 10 μ M	Veh	47.8611	39.70054	37.0625	34.65425	75
	Phe 50 μ M	Veh	42.9858	43.50406	33.2481	38.8336	74
	Phe 100 μ M	Veh	35.665	39.20873	26.2224	29.64496	72
	Veh	Cinn	31.6126	28.38982	80.8856	56.8805	77
	Phe 10 μ M	Cinn	46.5305	48.05924	111.9115	59.13319	75
	Phe 50 μ M	Cinn	41.8379	40.58716	98.3449	59.84014	75
	Phe 100 μ M	Cinn	36.2177	41.75295	53.9963	41.81652	75

* Mif (mifepristone), Spr (spironolactone), Par (paroxetine), Phe (phenylephrine). All cinnamon oil treatment is 7.41 ug/mL (~50 μ M) unless otherwise specified.

Supplemental Table 7. Whole-body cortisol level statistics after 50-sec white light illumination

Time after white light illumination	Mean cortisol (pg cortisol/mg protein)	Std. deviation	n
Ctrl (0 min)	2.83	0.61	5
2.5 min	7.35	1.31	4
5 min	10.08	2.86	4
10 min	10.88	2.71	5
15 min	11.02	2.25	4
20 min	3.34	0.68	4
30 min	2.75	0.86	5
60 min	3.02	0.74	5

Supplemental Table 8. Statistics of activated glucocorticoid receptor transcripts (EGFP transcript levels)

Genotype	Treatment	Mean $\Delta\Delta Ct$ value	Std. dev.	n
<i>mc2r</i> WT	Veh	0	0.2204	4
<i>mc2r</i> Het	Veh	0.4331	0.6013	8
<i>mc2r</i> Hom	Veh	-0.1063	0.3032	4
<i>mc2r</i> WT	ACTH	3.1280	0.4879	4
<i>mc2r</i> Het	ACTH	2.7009	0.3093	8
<i>mc2r</i> Hom	ACTH	-1.3100	0.2067	3
<i>mc2r</i> WT	Veh	0.0002	0.4291	5
<i>mc2r</i> Het	Veh	0.4153	0.7126	6
<i>mc2r</i> Hom	Veh	0.1590	0.1804	4
<i>mc2r</i> WT	CORT	5.6478	0.2443	4
<i>mc2r</i> Het	CORT	5.1863	0.2988	8
<i>mc2r</i> Hom	CORT	5.8217	0.3557	3

* ACTH (adrenocorticotrophic hormone) treatment was 10 μ M. CORT (cortisol) treatment was 10 μ M.

References

1. Neff KL, Argue DP, Ma AC, Lee HB, Clark KJ, Ekker SC. Mojo Hand, a TALEN design tool for genome editing applications. *BMC Bioinformatics*. 2013;14(1):1-1. doi:10.1186/1471-2105-14-1.
2. Cermak T, Doyle EL, Christian M, et al. Efficient design and assembly of custom TALEN and other TAL effector-based constructs for DNA targeting. *Nucleic Acids Research*. 2011;39(12):e82-e82. doi:10.1093/nar/gkr218.
3. Bedell VM, Wang Y, Campbell JM, et al. In vivo genome editing using a high-efficiency TALEN system. *Nature*. 2012;491(7422):114-118. doi:10.1038/nature11537.
4. Ma AC, Lee HB, Clark KJ, Ekker SC. High efficiency In Vivo genome engineering with a simplified 15-RVD GoldyTALEN design. *PLoS ONE*. 2013;8(5):e65259. doi:10.1371/journal.pone.0065259.
5. Ma AC, McNulty MS, Poshusta TL, et al. FusX: A Rapid One-Step Transcription Activator-Like Effector Assembly System for Genome Science. *Human Gene Therapy*. 2016;27(6):451-463. doi:10.1089/hum.2015.172.
6. Krug RG II, Poshusta TL, Skuster KJ, Berg MR, Gardner SL, Clark KJ. A transgenic zebrafish model for monitoring glucocorticoid receptor activity. *Genes, Brain and Behavior*. 2014;13(5):478-487. doi:10.1111/gbb.12135.
7. Lee HB, Schwab TL, Koleilat A, et al. Allele-Specific Quantitative PCR for Accurate, Rapid, and Cost-Effective Genotyping. *Human Gene Therapy*. 2016;27(6):425-435. doi:10.1089/hum.2016.011.